sequences comprise a sequence selected from the group consisting of AGTT, TATTC, TG, TTGA, TTGG, and GTACTGTT.

REMARKS

Applicants gratefully acknowledge the Examiner's indication in the Office Action that claim 22 is allowable. Claims 1-21 have been rejected in the Office Action. Claims 1, 16, 18 and 21 are amended herein and claims 24, 26 and 28 are canceled herein without prejudice or disclaimer to the subject matter herein to clarify the subject matter of the invention. Claims 1-23, 25 and 27 are now pending in this matter.

The foregoing claim amendments are intended to clarify the inventive subject matter and thereby overcome the rejections under 35 U.S.C. § 112, first and second paragraphs.

Basis for the claim amendments and newly added claims is found throughout the specification and specifically at page 7, line 37 to page 8, line 5 (for AGTT, TATTC, TG and GTACTGTT) and page 30, lines 18-27 (for TTGA and TTGG). The claim amendments bring the Sequence Listing into full compliance. No new matter is submitted by these claim amendments and no new issues are raised by the claim amendments. Accordingly, applicants respectfully submit that the claim amendments and newly added claims should be entered.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 1-21 and 23-28 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants submit that the claims prior to their amendment herein were definite because persons skilled in the art would have been readily able to ascertain the scope of the claimed invention. Nonetheless,

Applicants amended their claims in an effort to expedite prosecution of the application. The amendments are intended to merely add consistency to certain portions of the claims, and they are not related to patentability of the claims. The amended claims continue to satisfy the definiteness requirements of 35 U.S.C. § 112, second paragraph.

With regard to claims 1, 16 and 21, the phrase "a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified" has been deleted without prejudice or disclaimer. This obviates the Examiner's rejection based thereon.

With regard to claim 1, the term "said gene" has clear and positive antecedent basis in the previous phase "a gene in a selected organism or group of organisms". There is no other possible gene that said gene could be referring to. There is no ambiguity. A person of skill in the art would readily understand that "said gene" is the gene that one desires to optimize the expression of, consistent with the objects of the invention.

With regard to claim 16, the foregoing amendments obviate the Examiner's basis for rejection.

Claim 28 has been canceled without prejudice or disclaimer, thus obviating the Examiner's rejection based thereon.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-21 and 23-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At the outset, applicants respectfully point out that the initial burden of establishing a basis for denying patentability of a claimed invention rests upon the Patent Office. *See In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). It is equally well established that the Patent Office bears the initial burden to establish a reasonable basis to question the written description provided in the specification for the invention defined in Applicants' claims. *See In re Wright*, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993).

Applicants respectfully traverse the Examiner's rejection for the following reasons. Applicants' full scope of claimed subject matter was described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, prior to the amendment of the claims herein. Nonetheless, in the interest of advancing prosecution, applicants amended their claims. Applicants' claimed subject matter continues to be described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

It is well established that a disclosure of the specification provides a description of the claimed subject matter if it reasonably conveys to persons skilled in the art that the inventor has possession of that subject matter at the time the application was filed. *See, e.g., Fujikawa v. Wattanasin*, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) and *Vas-Cath, Inc.v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Applicants respectfully submit that their specification, as filed, satisfied that standard because persons of ordinary skill in the art, familiar with applicants' specification, would clearly understand that they possessed

the claimed subject matter. This is indicated, for example, by the Examiner's appreciation of the full scope of Applicants' claimed invention in the Office Action.

In the Office Action, the Examiner asserts that the claims "still encompass an enormous number of potential promoter sequences." Office Action, page 5, lines 16-18. In particular, while acknowledging that the claims are limited to specify conserved regions within the promoter set, the Examiner alleges that "there remains no structural/functional basis for one of skill in the art to envision those promoter sets that 1) retain the conserved sequences and 2) satisfy the functional limitations of the claim with regard to stepwise increments in promoter activity amongst the members of the promoter set for literally any cell type." Office Action, page 6, lines 1-5.

Contrary to the Examiner's assertions, the promoters of the set of promoters are structurally and functionally characterized. The functional limitations of the claims include the requirement that each promoter sequence of the set of promoters comprises a double stranded DNA sequence, the sense strands of which comprise at least two conserved sequences *identified in said organism or group of organisms* and the conserved sequences are restricted to specific sequences for prokaryotic and eukaryotic organisms, respectively, and the functional characterization being that any given set of promoters cover a range of promoter activities in steps, each step changing the B-galactosidase activity by 50-100%.

As it will be appreciated, the starting point for a person skilled in the art in setting out to construct a promoter set as claimed in a given organism is to identify at least two conserved sequences (as defined in the claims) in said organism. To identify such conserved sequences is well within the common knowledge of the skilled artisan and evidently, the measures to carry out such an identification using conventional methods are not dependent on the particular type or species of organism. After having provided a set of promoters wherein each promoter sequence comprises the conserved sequences as identified by randomly incorporating nucleotides in spacer sequences, the ordinarily skilled artisan may select a number of promoters to provide a set of

promoters having the functional characteristic of covering a range of promoter activities in steps, each step changing the B-galactosidase activity by 50-100%. Again, the selection of such a set of promoters does not require any inventive skills, but can be performed using conventional methods which are well know in the art.

As would also be appreciated, there are no difficulties in providing the claimed set of promoters for any given organism. The invention does not primarily lie in the construction of the set of promoters, but rather in that the inventor realized that (1) by randomly changing the sequence of spacer sequences, the promoter strength could be varied to provide promoters having a wide range of promoter activities and (2) the realization that the expression of a given gene in the selected organism could be optimized by replacing the natural promoter with one of the constructed promoter set and that the promoter resulting in an optimized expression of the gene is not, as generally believed in the art, necessarily that having the strongest promoter activity. The crux of the invention is, therefore, that it has become possible to optimize gene expression in any given organism using a set of promoters covering the range of activities as defined in the claims.

Further, the new Written Description Guidelines specify that one of the factors to be considered in determining if the written description requirement is satisfied is whether a representative number of species is disclosed in the specification. (See Guidelines, page 9). A representative number of species is disclosed if one skilled in the art would recognize that applicant possessed the necessary common attributes or features of the elements of the members of the genus in view of the species disclosed and claimed. *Id.*

As clearly demonstrated by a review of the specification, and contrary to the Examiner's assertion, applicants do indeed disclose such a representative number of species. For instance, Examples 1 and 2 on pages 17 to 27 of the specification specifically provide a set of promoter sequences for *L. lactis*, and Example 7 on pages 31-34 of the specification specifically provide a set of promoter sequences for *Saccharomyces*

cerevisiae. Further examples are provided concerning other bacteria, such as *Bacillus subtilis, Pseudomonas* and *E. coli*, and various exemplary methodologies for constructing the promoter sequences in accordance with the claimed invention, as well.

Moreover, the adequacy of the specification is further underscored by the fact that the methodology for determining β-galactosidase activity is provided in the specification on page 21 providing further evidence that applicants had possession of the claimed subject matter at the time the application was filed.

The phrases and terms which the Examiner deemed as new matter have been removed from the claims without prejudice or disclaimer thereto.

Applicants respectfully submit that the broad applicability of their invention reveals just the type of innovation the patent system seeks to encourage. To deny Applicants a patent on the basis that their invention may be applied to any desired organism is tantamount to denying them a patent because their invention is too effective and useful. Such a result is clearly contrary to United States patent law. Applicants have clearly established and described in their application an effective and well defined means for achieving their intended result along with a more than adequate number of illustrative examples. Therefore, a person of skill in the art would reasonably conclude applicants were indeed in possession of the claimed invention.

REQUEST FOR ALLOWANCE

For at least the reasons detailed above, the applicants respectively submit that all of the claims in the application are patentable. Favorable consideration, entry of this amendment, and issuance of a notice of allowance are respectively requested.

In the event any issues remain, the Examiner is encouraged to contact applicants' representatives to resolve such issues in an expeditious manner, and place the application in condition for allowance.

In the event any fees are incurred upon the filing of these documents, please charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,

HUNTON & WILLIAMS

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APPENDIX

1. (Thrice Amended) A set of promoter sequences suitable for optimizing the expression of a gene in a selected organism or group of organisms, said set of promoter sequences covering a range of promoter activities for said gene in small steps each step changing the activity by 50-100%, [with respect to promoter strength for said gene, a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified,] each promoter sequence of said set of promoter sequences comprising a double stranded DNA sequence, the sense strands of which comprise

at least two consensus sequences, said at least two consensus sequences corresponding to conserved sequences identified in said organism or group of organisms, at least half of each of said consensus sequences being kept constant in the set of promoter sequences, the at least two consensus sequences, when the selected organism or group of organisms is prokaryotic, being selected from the group consisting of TATAAT[, TATRAT,] and TTGACA [and an activator binding site upstream of the TATAAT sequence (a UAS) and the at least two consensus sequences,] when the selected organism or group of organisms is eukaryotic, being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box and, between said consensus sequences or flanking at least one of said consensus sequences, at least one nucleotide spacer sequence, at least part of

which, relative to the corresponding spacer sequence of the identified promoter, is varied by random incorporation of nucleotides that are selected from the group consisting of the nucleobases A, T, C and G[,

the set of promoter sequences covering the range of promoter activities for said gene, in steps, each step changing the activity by 50-100%].

16. (Thrice Amended) A method of constructing a set of promoter sequences which is suitable for optimizing the expression of a gene in a selected organism or group of organisms, the method comprising the steps of

(i) identifying in said organism or group of organisms a promoter sequence comprising at least two consensus sequences, which consensus sequences correspond to conserved sequences identified in said organism or group of organisms, at least one of the consensus sequences being flanked by a non-conserved nucleotide spacer sequence or both or said consensus sequences being separated by the non-conserved nucleotide spacer sequence, the at least two consensus sequences, when the selected organism or group of organisms is prokaryotic, being selected from the group consisting of TATAAT, TTGACA and an activator binding site upstream of the TATAAT sequence, when the selected organism or group of organisms is eukayotic, being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box,

(ii) constructing a set of single stranded DNA sequences each of which comprises [comprising] at least half of each of the consensus sequences, and a non-conserved nucleotide spacer sequence, at least part of which is varied by a random incorporation of nucleotides selected from the group consisting of the nucleobases A, T, C and G, whilst keeping the at least half of the consensus sequences constant, and

(iii) converting the single stranded DNA sequences into double stranded DNA sequences to obtain the set of promoter sequences covering a range of promoter activities for said gene[, with respect to promoter strength, a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified].

18. (Four Times Amended) A method of controlling in an organism the flux of a cellular metabolite or the expression of a desired gene product, said method comprising at least one step of changing the expression level of at least one gene in the pathway leading to formation of said metabolite or the expression level of said desired gene product, the step comprising

(i) selecting from the set of promoter sequences of claim 1 a plurality of promoter sequences covering a range of promoter activities for said gene, in steps, each step changing the β-galactosidase activity by 50-100% [a desired range of promoter activities],

(ii) transforming said set of promoter sequences into cells of the organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical

clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product.

21. (Four Times Amended) A method of isolating a promoter sequence being capable of optimizing the expression of a gene in a selected organism, the method comprising

(i) constructing, using the method of claim 16, a set of promoters covering a range of promoter activities for said gene, in steps, each step changing the B-galactosidase activity by 50-100%, [with respect to promoter strength, a range of promoter activities which is within a range from the weakest activity that is detectable by inserting each of the set of promoters into a vector comprising a promoterless β-galactosidase reporter gene system, transforming a host strain with the resulting vector and cultivating the transformed host strain with the resulting vector and cultivating the transformed host strain to express β-galactosidase from the reporter gene and identifying that promoter set showing the weakest β-galactosidase activity, to the strongest activity that is detectable by the same procedure with the exception that the promoter of the promoter set showing the strongest activity in said reporter gene system is identified,]

(ii) transforming said set of promoters into cells of the selected organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a

lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product, and

(iv) isolating said promoter sequence from the clone.

23. (Amended) A set of promoters according to claim 1 [where in the at least two consensus sequences, the activator binding site upstream of the TATAAT sequence is] suitable for optimizing the expression of a gene in a prokaryotic organism wherein the promoter sequences comprise a sequence selected from the group consisting of AGTT, TATTC, TG, TTGA, TTGG, [TTAGCACTC and GAGTGCTAA] and GTACTGTT.